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On the relevance of face-to-edge $\pi-\pi$ interactions to chiral recognition

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Abstract

Several chiral selectors have been developed in our laboratory on the premise that a cleft having an electron-deficient aromatic system as a "wall" and an electron-rich aromatic system as a "floor" would be conducive to chiral recognition. As a test of this hypothesis, six racemates, **5a–c** and **6a–c**, each containing electron-deficient and electron-rich aromatic systems, were prepared and studied chromatographically on a chiral stationary phase derived from the N,N-diallyl amide of naproxen. The *endo* stereoisomers, **5a–c**, contain the aforementioned clefts whereas the *exo* stereoisomers, **6a–c**, do not. The enantiomers of the former show much larger separation factors than do the enantiomers of the latter, supportive of the importance of the preorganized cleft. For comparative purposes, chromatographic data are provided for the enantiomers of both the selector used in the commercially available CSP 1 and its *trans* isomer.

Keywords: Chiral stationary phases, LC; Enantiomer separation; $\pi-\pi$ Interactions; Phenanthrenes

1. Introduction

The increasing demand for enantioselective technologies has led to a general awareness of the importance of chiral stationary phases (CSPs) for chromatographic enantioseparations [1,2]. While many useful CSPs have been developed empirically from naturally occurring materials such as proteins or polysaccharides [1], CSP design can be approached from a mechanistic standpoint. For many years, we have been committed to the attainment of a better understanding of the processes by which analyte enantiomers are differentiated by a chiral stationary phase. In several instances, chiral stationary phases specifically targeted for the enantiomers of economically important pharmaceuticals have been developed [3,4]. For example, CSP 1, known commercially as the Whelk-O 1 and available in either enantiomeric form, was initially designed for the enantioseparation of underivatized naproxen. This CSP has proven to be capable of separating the enantiomers of a broad spectrum of analyte enantiomers [5]. The success of CSP 1 has been attributed to the presence of a highly preorganized chiral cleft containing three functional groups essential to the chiral recognition of analytes having certain structural features. The cleft consists of a π-basic aromatic substituent to serve as a "floor" and a π-acidic 3,5-dinitrobenzamide group to serve as a "wall". The dinitrobenzamide NH serves as a hydrogen bond donor. A π-basic group in the analyte is thought to enter the cleft and undergo simultaneous face-to-

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edge and face-to-face $\pi-\pi$ interactions. Hydrogen bond acceptor sites in the analyte may interact with the CSP's NH. The enantiomer which can undergo these interactions simultaneously, without having to deviate substantially from the conformation(s) preferentially populated prior to interaction with the CSP, is expected to be preferentially retained.

The preceding mechanistic rationale leads one to expect that the scope of CSPs 2 and 3 should resemble that of CSP 1 in so far as these CSPs have similar clefts (Fig. 1). In the course of preparing the selectors for CSPs 2 and 3, other stereoisomers of these selectors were obtained, some of which lack the aforementioned cleft. By chromatographing the various racemic stereoisomers on a CSP believed to be sensitive to the presence (or absence) of this cleft, we expected the chromatographic data to provide some indication of whether the cleft truly plays an important role in the chiral recognition of these analytes and, by extension, of CSPs having such clefts. The chromatographic evaluation was performed on naproxen-derived CSP 4 [6].

2. Experimental

2.1. General

All ^{1}H NMR spectra were recorded on a Varian XL-200 FT NMR instrument operating at 200 MHz. Chemical shifts are reported in ppm (δ) relative to tetramethylsilane as the internal standard. Chromatography was performed at room temperature using a Rainin HPX Rabbit pump, a Rheodyne Model 7125 injector with a 20-μl sample loop, a Milton Roy-LDC UV detector (254 nm) and a Shimadzu CR1A integrating recorder. The void volumns were determined by injecting 1,3,5-tri-*tert.*-butylbenzene. Signs of optical rotation were determined with an Autopol III Automatic Polarimeter as an online chiroptic detector.

All chemicals used were of reagent grade. Chromatographic solvents were EM Science HPLC grade. Analytes **5a–c** and **6a–c** (Fig. 2) were prepared by methods reported previously [7,8]. Characterization data for those not described heretofore are provided.

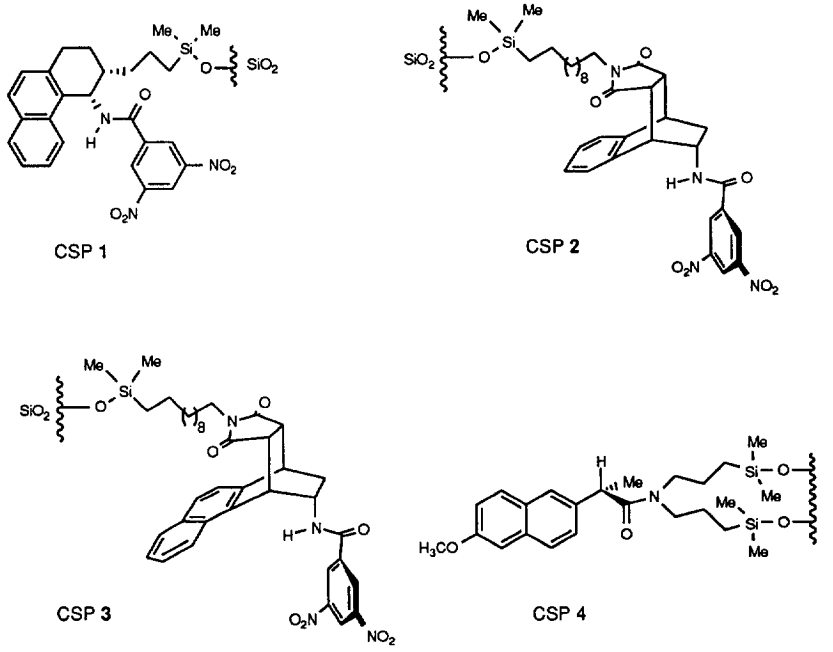


Fig. 1. Structures of CSPs 1, 2, 3 and 4.

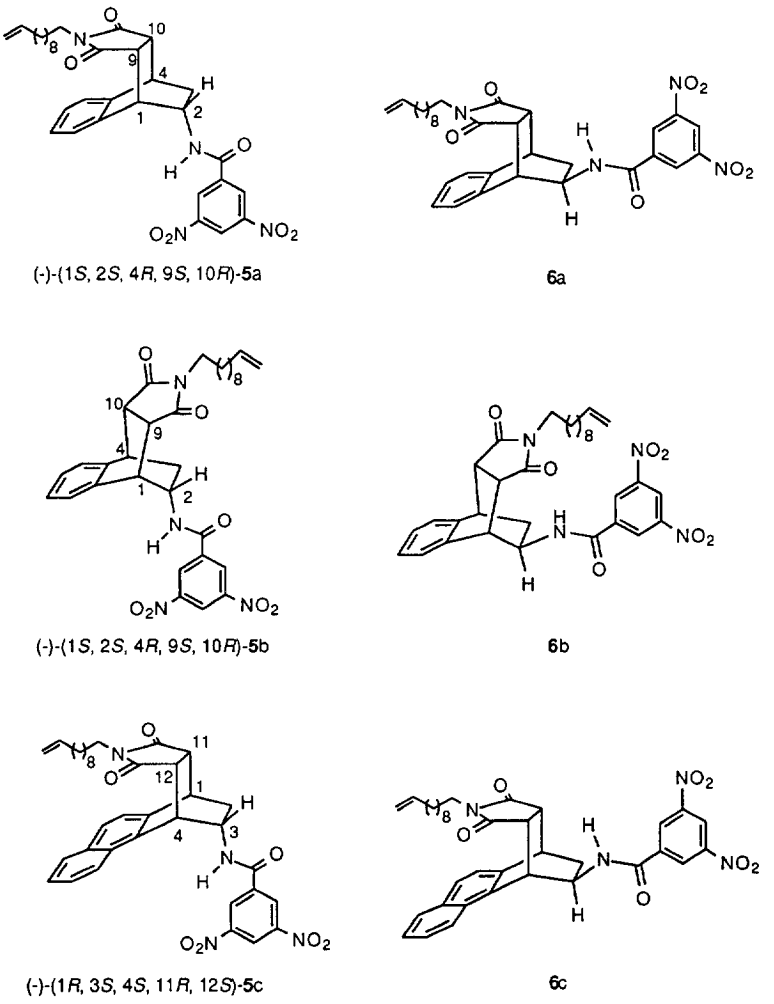


Fig. 2. The structures of the analytes **5a–c** and **6a–c** used for this study. Absolute configurations for **5a–c** are assigned as shown.

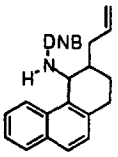
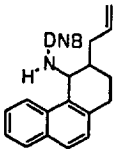
*2.1.1. 1,4-Ethano-2-endo-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydronaphthalene-9,10-exo-ω-undecenylimide ((±)-**5b**)*

^{1}H NMR (200 MHz, C^2HCl_3) δ: 9.11 (1H, t, J=1.7 Hz), 8.72 (1H, d, J=1.7 Hz), 7.40–7.12 (4H, aromatic), 7.06 (1H, amide proton, d, J=7.7 Hz), 5.81 (1H, m), 5.05–4.91 (2H, m), 4.75 (1H, m), 3.82 (1H, m), 3.71 (1H, m), 3.31–2.90 (4H), 2.60 (1H, m), 2.04 (2H, m), 1.80–0.79 (15 H). MS (HR–FAB) calculated for $C_{32}H_{37}N_4O_7$ [M+1] 589.2662, found 589.2660.

*2.1.2. 1,4-Ethano-2-exo-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydronaphthalene-9,10-endo-ω-undecenylimide ((±)-**6a**)*

^{1}H NMR (200 MHz, C^2HCl_3) δ: 9.19 (1H, t, J=1.6 Hz), 9.02 (1H, d, J=1.6 Hz), 7.29–7.12 (4H, m), 6.74 (1H, amide NH, d, J=9.6 Hz), 5.80 (1H, m), 5.00 (1H), 4.90 (1H), 4.28 (1H, m), 3.93 (1H, m), 3.69 (1H, m), 3.35(1H, dd, J=9.4 Hz, 4.5 Hz), 3.21 (1H, dd, J=9.4 Hz, 4.5 Hz), 3.07 (2H, m), 2.42 (1H, m), 2.05 (2H, m), 1.63–0.90 (11H), 0.73 (4H).

Table 1
Separation of the enantiomers of the *endo* and *exo* stereoisomers on CSP 4

Racemate[a]	k_1'	α	More retained enantiomer
endo **5**a	4.17	3.44	(+)-1*R*, 2*R*, 4*S*, 9*R*, 10*S*
5b	4.17	3.48	(+)-1*R*, 2*R*, 4*S*, 9*R*, 10*S*
5c	6.80	5.84	(+)-1*S*, 3*R*, 4*R*, 11*S*,12*R*
exo **6**a	4.58	1.13	–
6b	12.3	1.18	–
6c	8.07	1.25	–
cis 	6.47	5.38	(+)-3*S*, *4R*
trans 	4.98	4.28	(+)-*3R*, *4R*

Mobile phase: 20% 2-propanol in hexane; flow-rate: 2 ml/min.
[a]*endo* and *exo* refer to the spatial relationship between the π-acidic group (3,5-dinitrobenzamido) and the π-basic group (benzo or naphtho) in the analytes. The underlined stereochemical descriptor is that of the stereogenic center bearing the nitrogen. Signs of optical rotation were determined at 589 nm.

MS (HR–FAB) calculated for $C_{32}H_{37}N_4O_7$ [M+1] 589.2662, found 589.2660.

*2.1.3. 1,4-Ethano-2-exo-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydronaphthalene-9,10-exo-ω-undecenylimide ((±)-**6b**)*

^{1}H NMR (200 MHz, C^2HCl_3) δ: 9.21 (1H, t, J=1.7 Hz), 9.06 (1H, d, J=1.7 Hz), 7.40–7.15 (4H, aromatic), 5.76 (1H, m), 5.58 (1H, amide NH, d, J=7.6 Hz), 5.05–4.87 (3H), 4.25 (1H, m), 3.78 (1H, m), 3.34–3.30 (4H), 2.71 (1H, m), 2.01 (2H, m), 1.70–0.90 (15H). MS (HR–FAB) calculated for $C_{32}H_{37}N_4O_7$ [M+1] 589.2662, found 589.2661.

*2.1.4. 1,4-Ethano-3-exo-(3,5-dinitrobenzamido)-1,2,3,4-tetrahydrophenanthrene-11,12-endo-ω-undecenylimide ((±)-**6c**)*

^{1}H NMR (200 MHz, C^2HCl_3) δ: 9.21 (1H, t, J=1.8 Hz), 9.18 (1H, d, J=1.8 Hz), 8.11 (1H, d, J=8.3 Hz), 7.81 (1H, d, J=8.4 Hz), 7.77 (1H, d, J=8.2 Hz), 7.61–7.42 (2H, aromatic), 7.32 (1H, d, J=8.3 Hz), 6.85 (1H, amide proton, d, J=7.7 Hz), 5.82 (1H, m), 5.05–4.91 (2H, m), 4.81 (1H, m), 4.28 (1H, m), 3.88 (1H, m), 3.47 (1H, dd, J=9.1 Hz, 3.5 Hz), 3.30 (1H, dd, J=9.1 Hz, 3.5 Hz), 2.93 (2H, m), 2.47 (1H, m), 2.05 (2H, m), 1.68 (1H, m), 1.50–1.01 (6H), 0.93–0.60(4H), 0.48–0.35 (4H). MS (HR–FAB) calculated for $C_{36}H_{39}N_4O_7$ [M+1] 639.2819, found 639.2821.

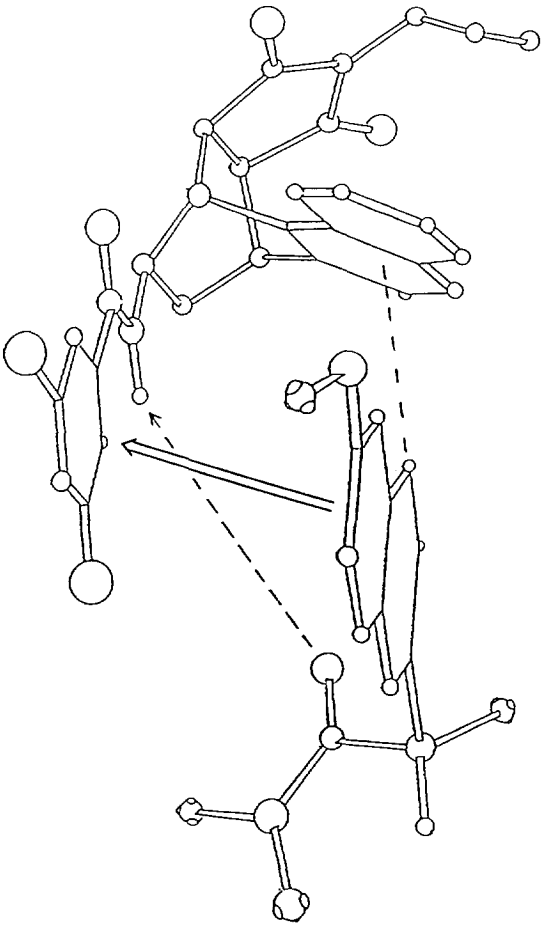


Fig. 3. A chiral recognition model for the more stable diastereomeric complex between a soluble analog of (1*S*, 3*R*, 4*R*, 11*S*, 12*R*)-CSP 3 and (*S*)-naproxen diallyl amide. Three simultaneous non-covalent bonding interactions are shown as π–π face-to-face stacking, π–π face-to-edge interaction and hydrogen bonding interaction.

2.1.5. trans-4-(3,5-Dinitrobenzamido)-3-allyl-1,2,3,4-tetrahydrophenanthrene

^{1}H NMR (200 MHz, C^2HCl_3) δ: 9.11 (1H, t, J=2.4 Hz), 8.87 (1H, d, J=2.4 Hz), 7.89 (1H, d, J=8.8 Hz), 7.83 (1H, d, J=9.6 Hz), 7.78 (1H, d, J=8.4 Hz), 7.52–7.43 (2H), 7.30 (1H, d, J=8.4 Hz), 6.58 (amide NH, d, J=9.6 Hz), 6.00–5.78 (2H), 5.13–5.05 (2H), 3.05–2.98(2H), 2.49–1.99 (5H). MS (HR–FAB) calculated for $C_{24}H_{22}N_3O_5$ [M+1] 432.1559, found 432.1559.

3. Results and discussion

Face-to-edge $\pi-\pi$ interaction, which is electrostatic in nature and involves the attraction of a proton(s) of one aromatic group to the electron-rich center of another, has been observed as the dominant motif in crystals of simple aromatics [9]. This type of non-covalent relationship has also been routinely seen in proteins and has significant influence over their tertiary structures [10,11]. It seems reasonable to suppose that face-to-edge interactions can be used in the design of chiral selectors. However, one will have to learn how the various interaction sites must be arranged spatially to afford the best results in terms of scope and efficacy. This study is a step in that direction.

Data from the chromatographic evaluation of the six racemic stereoisomers, **5a–c** and **6a–c**, obtained using CSP 4, are presented in Table 1. Large separation factors are found for the enantiomers of the three cleft-containing *endo* isomers, **5a–c**, whereas the enantiomers of *exo* isomers **6a–c** show relatively small separation factors. The significant differences in enantioselectivity of the *endo* and *exo* stereoisomers is taken to indicate the importance of the preorganized clefts to the chiral recognition of the *endo* isomers. As expected, the enantiomers of **5c** show the largest separation and retention factors owing to the greater π-basicity of the naphthyl system. For comparative purposes, the enantiomers of the selector used in CSP 1 and those of its *trans* isomer were similarily chromatographed. The separation factor noted for the enantiomers of **5c** is slightly greater than that noted for the enantiomers of the selector used in CSP 1.

Fig. 3 depicts the relative orientations of the N,N-dimethylamide of (*S*)-naproxen, a close analog of (*S*)-CSP 4 shown in a low energy conformation, and the enantiomer of **5c** expected to be more strongly complexed. This orientation is consistent with NMR studies, the details of which will be reported subsequently. On the basis of this mechanistic picture, the absolute configurations of the enantiomers of **5a–c** most retained by (*S*)-CSP 4 are assigned as (+)-(1*R*,2*R*,4*S*,9*R*,10*S*)-**5a**, (+)-(1*R*,2*R*,4*S*,9*R*,10*S*)-**5b**, and (+)-(1*S*,3*R*,4*R*11*S*12*R*)-**5c**. No absolute configurations are assigned for *exo* isomers **6a–c**.

4. Conclusions

Six racemic stereoisomers (**5a–c** and **6a–c**) were prepared and chromatographically evaluated on a π-basic chiral stationary phase derived from (*S*)-naproxen diallyl amide. The enantiomers of the stereoisomers which contain a preorganized cleft show significantly larger separation factors than do those which lack these clefts. These chromatographic data provide strong support for a chiral recognition rationale which entails face-to-edge $\pi-\pi$ interaction in conjunction with hydrogen bonding and face-to-face $\pi-\pi$ interaction. On the basis of the rationale, absolute configurations are assigned to **5b** and **5c**, that of **5a** having been assigned previously [7].

Acknowledgments

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